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Full-length Article

Large-scale study of *Toxoplasma* and Cytomegalovirus shows an association between infection and serious psychiatric disorders

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ABSTRACT

Background: Common infectious pathogens have been associated with psychiatric disorders, self-violence and risk-taking behavior.

Methods: This case-control study reviews register data on 81,912 individuals from the Danish Blood Donor Study to identify individuals who have a psychiatric diagnosis (N = 2591), have attempted or committed suicide (N = 655), or have had traffic accidents (N = 2724). For all cases, controls were frequency matched by age and sex, resulting in 11,546 participants.

Plasma samples were analyzed for immunoglobulin G (IgG) antibodies against *Toxoplasma gondii* and cytomegalovirus (CMV).

Results: T. gondii was detected in 25·9% of the population and was associated with schizophrenia (odds ratio [OR], 1·47; 95% confidence interval [CI], 1·03–2·09). Accounting for temporality, with pathogen exposure preceding outcome, the association was even stronger (IRR, 2·78; 95% CI, 1·27–6·09). A very weak association between traffic accident and toxoplasmosis (OR, 1·11; 95% CI, 1·00–1·23, p = 0.054) was found.

CMV was detected in 60·8% of the studied population and was associated with any psychiatric disorder (OR, 1·17; 95% CI, 1·06–1·29), but also with a smaller group of neurotic, stress-related, and somatoform disorders (OR, 1·27; 95% CI, 1·12–1·44), and with attempting or committing suicide (OR, 1·31; 95% CI, 1·10–1·56). Accounting for temporality, any psychiatric disorder (IRR, 1·37; 95% CI, 1·08–1·74) and mood disorders (IRR, 1·43; 95% CI, 1·01–2·04) were associated with exposure to CMV. No association between traffic accident and CMV (OR, 1·06; 95% CI, 0·97–1·17) was found.

Conclusions: This large-scale serological study is the first study to examine temporality of pathogen exposure and to provide evidence of a causal relationship between *T. gondii* and schizophrenia, and between CMV and any psychiatric disorder.

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1. Introduction

In recent years there has been a growing interest in the influence of infectious agents on human behavior and mental disorders. Common infectious pathogens such as *Toxoplasma gondii* (*T. gondii*) and cytomegalovirus (CMV) have been associated with psychiatric disorders, cognitive deficits, suicidal behavior, and traffic accidents (Dickerson et al., 2018, 2017, 2014b; Flegr et al., 2002; Flegr and Horáček, 2018; Hamdani et al., 2017; Sutterland et al., 2015). The nature of these associations remains uncertain, but it is plausible that they reflect causality.

T. gondii is a protozoan parasite that causes the disease toxoplasmosis. Most exposed people experience a latent (asymptomatic) form of the disease. However, prenatal infection with *T. gondii* may cause abortion as well as a congenital syndrome that includes seizures and severe intellectual disability (Nissen et al., 2017). Studies have demonstrated that latent *T. gondii* infection may induce behavioral changes both in animal models and in humans, possibly as part of an evolutionary strategy dubbed the 'parasite manipulation hypothesis', but the results have been inconsistent (Flegr et al., 2011; Poirotte et al., 2016; Worth et al., 2014).

CMV is a common lifelong, latent beta herpes virus infection, and most healthy exposed people experience a latent form of the disease, with few or no symptoms. Congenital CMV infection may cause visual impairment, hearing loss or cognitive impairment (Dollard et al., 2007). Several studies have shown that infection with CMV is associated with increased risk of psychiatric disorders such as schizophrenia, bipolar disorder, and cognitive deficits (Dickerson et al., 2014b; Hamdani et al., 2017). Moreover, CMV may exacerbate existing psychiatric pathology through mechanisms including induction of pro-inflammatory cytokines (e.g., interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α)) or directly via interactions with specific illness susceptibility genes (Prossin et al., 2015).

If *T. gondii* and CMV infections were causally associated with inexpedient behavior or psychiatric disorders it could have public health as well as clinical implications, since it could offer targets for both prevention and treatment. To this end, it is essential to establish the direction of the association between the infectious agents and the behavioral and psychiatric outcomes, i.e. the sequence of events. We therefore examined a large cohort of blood donors carefully assessed for both *T. gondii* and CMV infection exposures over time, and for behavioral and psychiatric outcomes.

2. Methods

2.1. Study population

The Danish Blood Donor Study (DBDS) is an ongoing national large-scale prospective cohort of Danish blood donors, previously described (Burgdorf et al., 2017). DBDS was initiated in March 2010 as a multicenter, public-health study and biobank (www.dbds.dk) and by 2018 included more than 110,000 individuals between 18 and 67 years at day of inclusion (inclusive). Data collection in DBDS employs existing infrastructure for standardized data collection and for handling and storage of blood samples from all Danish blood centers. The DBDS biobank contains DNA and EDTA plasma samples, consecutive for all donors returning for blood donation after enrolment.

2.2. Overall design

We carried out a case-control study in DBDS and a case-control study nested in DBDS to account for temporality, i.e., the exposure should precede the outcome of interest. Specifically, we identified all individuals in the DBDS cohort registered with psychiatric disorders, suicidal behavior, or traffic accidents (N = 5953). All cases with psychiatric disorders (1971–2013), suicidal behavior (1977–2011) and traffic accidents (2008–2012) were included. These were frequency matched with suitable controls (N = 7101). For all identified individuals, sample immunological assays were used to provide information on past infection with *T. gondii* and CMV. Details follow below.

2.3. Psychiatric diagnoses

The Danish Psychiatric Central Research Register (Mors et al., 2011) is a nationwide computerized register. The register holds information on all admissions to Danish psychiatric inpatient facilities since 1969 and to outpatient facilities since 1995. Psychiatric diagnoses are coded according to the International Classification of Diseases − 8th Revision (WHO, 1965) between 1969 and 1993 and 10th Revision (WHO, 1994) since 1994.

Cases with any diagnosis of psychiatric disorder (ICD-10: F00-F99 and eq. ICD-8) and subgroups of cases, including schizophrenia and related disorders (ICD-10: F20-F29 and eq. ICD-8 (Pedersen et al., 2014)), mood disorders (ICD10: F30-F39 and eq. ICD8) and neurotic, stress-related, and somatoform disorders (ICD-10: F40-F48 and eq. ICD-8) before the end of 2013 were obtained. For all participants, we obtained information on parental history of any psychiatric diagnosis.

2.4. Attempting and committing suicide

The Danish Register of Causes of Death (Juel and Helweg-Larsen, 1999) contains information concerning all residents who died in Denmark from 1970 through 2011. In Denmark, the legal regulation on death certification states that any case of sudden and unexpected death shall be reported to the police, and the death certificate may only be issued after a medico-legal examination.

The Danish National Patient Register (Lynge et al., 2011) was established in 1977 to prospectively record public hospital admissions, and obtained nationwide coverage regarding inpatient admissions. From 1995 it was expanded to include outpatient and emergency room contacts, and from 2002 it includes private hospitals and private specialty clinics. Diagnoses are based on the International Classification of Diseases 8th Revision between 1977 and 1993, and the International Classification of Diseases –10th Revision from 1994 onward.

First episode of deliberate self-violence and suicide were defined by inclusion in the Danish National Patient Register (1977–2012), the Psychiatric Central Research Register (1969–2013) or the Danish Register of Causes of Death (1970–2011), which has previously been used in Danish register studies (Nordentoft, 2011). In this study we restricted the definition criteria to episodes registered after the age of 15.

2.5. Traffic accidents

Participants who had been involved in a traffic accident in the period 2008–2012 were identified in the Danish National Patient Register or in the Danish Register of Causes of Death.

Participants registered with accident as a cause of contact in the Danish National Patient Register were defined as a case if they had one or more cause of contact that indicated involvement in a traffic accident (diagnosis ICD-10: Z041, accident-code: EUK0, EUG0 plus EUA0 or EUA2 or EUHD01). Cases registered as a pedestrian (EUP1) or passenger (EUHD02, EUT2-EUT5) were excluded. Participants with

transport accidents (ICD-10: V01-V99) as an underlying cause of death from the Danish Register of Causes of Death were also defined as cases.

2.6. Controls

Frequency matched controls were selected among the 81,912 DBDS participants and matched for age (age at time of blood sampling in completed years) and sex for the 5953 cases. For each sex and age matched group, 20% more controls than cases were chosen (N = 7101, of whom 554 were also a case) giving a total number of 12,500 cases and controls. To allow using controls between different outcomes, controls were not conditioned to be healthy. This was handled in the specific analyses for each outcome.

2.7. Immunological assays

Plasma samples from blood donations were initially collected in 5 ml plasma preparation tubes (K2EDTA/Gel), centrifuged and frozen within 6 h after blood collection. For this study all 81,912 plasma samples were thawed and transferred to Thermo Scientific Matrix tubes with 2D Codes on the bottom, before selection of cases and controls.

The 12,500 selected plasma samples for cases and controls were randomized into three batches and transferred to the Stanley Neurovirology Laboratory for analysis of specific enzyme-based immunoassays for immunoglobulin (IgG) class antibodies against *T. gondii* and CMV, previously described (Dickerson et al., 2003). The raw IgG antibody titer values were standardized across plates and the distribution of this standardized z-score was fitted with two normal distributions to determine the cut-off value for each batch and each infectious agent (Supplemental Figs. 1 and 2). The cut-off was determined to match the area under the tails in the two normal distributions. If the individual had a value above this cut-off, it was considered that the person had been exposed to the infectious agent.

2.8. Statistical methods

After sample-analysis and quality control, statistical analysis was conducted on 11,546 cases and controls.

A conditional logistic regression model was used to analyze the associations between *T. gondii* and CMV and the risk of psychiatric disorders, suicidal behavior, and traffic accidents forming strata for frequency matched sets. By design, we controlled for sex and age at time of blood sampling, therefore age and sex are not directly included in the conditional logistic regression. Additionally, we conducted an analysis where toxoplasmosis and CMV were mutually adjusted, and all analyses were adjusted for parental history of psychiatric disorder before time of blood collection, as previously described (Pedersen et al., 2011). Odds ratios (ORs) and 95% likelihood ratio confidence intervals (95% CIs) were calculated. A two-sided P value of less than 0·05 was considered to be statistically significant. Statistical analyses were performed using the PHREG procedure in SAS 9·3 (SAS Institute, Cary, North Carolina). We also calculated the batch specific estimates (Supplemental Figs. 3 and 4).

The nested case-control study was conducted to account for temporality, i.e., the exposure should precede the outcome of interest to fulfill Hills viewpoints of causality (Rothman et al., 2008). For each outcome of interest, we included only individuals with onset after the date of blood sample collection and conducted conditional logistic regression for these cases and their time-, age- and sex-matched controls. The estimates thus obtained are informative for the risk of developing the outcomes of interest following exposure to *T. gondii* or CMV i.e., incidence rate ratios (Pearce, 1993; Vandenbroucke and Pearce, 2012).

2.9. Ethics

The Ethics Committee of Central Denmark (M-20090237) and The Danish Data Protection Agency (2007-58-0015) have previously approved the study. The Danish Data Protection Agency approved the transport and analysis of plasma samples to the Stanley Neurovirology Laboratory. The National Board of Health approved the use of registry data. Data will be kept confidential under the law concerning processing of personal data. Written informed consent was obtained from all participants.

3. Results

Register data on 81,912 individuals were reviewed to find individuals who had been diagnosed with psychiatric disorders, had attempted or committed suicide, and/or had been involved in traffic accidents, resulting in a total of 12,500 cases and controls. After sample analysis and quality control, statistical analysis was conducted on 11,546 cases and controls, see distribution of cases and controls (non-exclusive) in Table 1. A total of 5492 individuals (2807 women) were registered with a psychiatric disorder, suicide or suicide attempt, or traffic accident. Overall, 2591 individuals (1314 women) were registered in the Danish Psychiatric Central Research Register with a

Table 1
Odds ratios and incidence rate ratios of toxoplasmosis and CMV on psychiatric disorders, suicide and traffic accident.

	Case-control study Odds ratios				Nested case-control study Incidence rate ratios*			
	Case N	Control N	*T. gondii* OR (95%CI)	CMV OR (95%CI)	Case N	Control N	*T. gondii* IRR (95%CI)	CMV IRR (95%CI)
Any psychiatric disorders (F00-F99)	2,591	6,331	1·03 (0·93;1·15)	**1·17 (1·06;1·29)**	325	5,109	1·05 (0·80;1·38)	**1·37 (1·08;1·74)**
Schizophrenia and related disorders (F20-F29)	151	6,550	**1·47 (1·03;2·09)**	1·25 (0·89;1·77)	28	5,293	**2·78 (1·27;6·09)**	1·34 (0·61;2·92)
Mood disorders (F30-F39)	711	6,501	0·89 (0·73;1·07)	1·09 (0·92;1·28)	147	5,254	0·92 (0·61;1·38)	**1·43 (1·01;2·04)**
Neurotic, stress-related, and somatoform disorders (F40-F48)	1,385	6,430	1·05 (0·92;1·21)	**1·27 (1·12;1·44)**	208	5,192	1·09 (0·78;1·51)	1·20 (0·89;1·60)
Suicide or suicide attempt	655	6,503	1·13 (0·94;1·36)	**1·31 (1·10;1·56)**	23	5,259	0·45 (0·13;1·55)	1·18 (0·50;2·82)
Traffic accident	2,724	6,294	1·11 (1·00;1·23)	1·06 (0·97;1·17)	751	5,228	1·18 (0·99;1·41)	1·15 (0·98;1.35)

Adjusted for sex and age due to design and parental history of psychiatric disorder.
'bold' indicates a likelihood ratio based 95% p-value < 0·05
'*' We accounted for temporality by excluding individuals with outcome of interest before the date of blood sample collection, i.e. past infection with *T. gondii* and CMV should precede the outcome of interest, estimating incidence rate ratios.

psychiatric diagnosis, 655 (377 women) had attempted or committed suicide, and 2724 individuals (1233 women) had been involved in a traffic accident. The average age at blood donation was 37.4 years in the study population; age distribution is shown in Supplemental Fig. 5.

3.1. Infection with T. gondii and CMV

Of the 11,546 studied individuals, 2990 and 7020 individuals, respectively, tested positive for IgG class antibodies against *T. gondii* (25·9%) or CMV (60·8%). For a more detailed overview of the number of infected/non-infected cases and controls for each health outcome, see Supplemental Table 1.

We found that individuals with a *T. gondii* infection had increased odds of being diagnosed with schizophrenia disorders compared to those without infection (OR, 1·47; 95% CI, 1·03–2·09) (Table 1). The association was even stronger when accounting for temporality and considering only the 28 cases who were diagnosed with a schizophrenia disorder after the date of blood collection (IRR, 2·78; 95% CI, 1·27–6·09) (Table 1). A very weak association between toxoplasmosis and involvement in traffic accidents was observed in 9018 individuals (OR, 1·11; 95% CI, 1·00–1·23) also when including only individuals with traffic accident after blood donation (IRR, 1·18; 95% CI, 0·99–1·41) (Table 1). Besides schizophrenia, *T. gondii* infection was not statistically significantly associated with any other psychiatric disorder, whether overall (OR, 1·03; 95% CI, 0·93–1·15), or more specifically, i.e. mood disorders (OR, 0·89; 95% CI, 0·73–1·07), neurotic, stress-related, and somatoform disorders (OR, 1·05; 95% CI, 0·92–1·21), or attempting or committing suicide (OR, 1·13; 95% CI, 0·94–1·36) (Table 1).

CMV infection was associated with increased risk of: any psychiatric disorder (OR, 1·17; 95% CI, 1·06–1·29), neurotic, stress-related and somatoform disorders (OR, 1·27; 95% CI, 1·12–1·44) and attempting or committing suicide (OR, 1·31; 95% CI, 1·10–1·56) (Table 1). Considering only cases with an outcome after the date of blood donation, CMV infection was still statistically significantly associated with any psychiatric disorder (IRR, 1·37; 95% CI, 1·08–1·74) but not with attempting or committing suicide (IRR, 1·18; 95% CI, 0·50–2·82). In addition, CMV infection was found only to be associated with mood disorders (IRR, 1·43; 95% CI, 1·01–2·04) after excluding individuals with onset pre-dating blood sample collection (Table 1). CMV infection was not statistically significantly associated with schizophrenia and related disorders (OR, 1·25; 95% CI, 0·89–1·77) or with traffic accidents (OR, 1·06; 95% CI, 0·97–117) (Table 1). Mutual adjustment of CMV and toxoplasmosis did not change the overall findings (Supplemental Table 2).

4. Discussion

This largest to date serological study provides evidence that exposure to *T. gondii* might be a contributing causal factor for developing schizophrenia and that exposure to CMV might be a contributing causal factor for developing serious psychiatric disorders.

Research suggests that changes in dopamine levels are involved in the pathogenesis of toxoplasmosis-associated behavior changes in humans. These include prolongation of reaction time, decreased long-term concentration, decreased cognition and specific changes in neurodegenerative- and psychiatric disorders (Flegr et al., 2003).

The *Toxoplasma* genome carries two genes encoding dopamine-synthesizing enzymes (tyrosine hydroxylase) (Gaskell et al., 2009; Henriquez et al., 2009). Dopamine is produced and secreted in large amounts in *Toxoplasma* cysts in the brain tissue of infected rodents (Martin et al., 2015; Prandovszky et al., 2011) and most likely in humans as well (Flegr et al., 2003; Henriquez et al., 2009; McConkey et al., 2013; Skallová et al., 2005). It has been shown that latent (but not acute) *T. gondii* infection in mice elevates the local brain dopamine concentrations, as observed in individuals with schizophrenia (Eyles et al., 2012; Henriquez et al., 2009). This increased dopamine level may be responsible for toxoplasmosis-associated behavior changes.

Human cognition may be affected by exposure to *T. gondii*, as severe congenital toxoplasmosis can lead to mental retardation (Nissen et al., 2017). Even among "unaffected" children with congenital toxoplasmosis, high maternal antibody titres during pregnancy are associated with delayed mental development in their first year and an increased risk of having an IQ less than 70 at 7 years (Sever et al., 1988). Human cognition and behavior may also be affected by postnatal *T. gondii* infection. In schoolchildren, *Toxoplasma* seropositivity has been associated with lower mathematics (Ferreira et al., 2013) and reading skills but also poorer memory capacity (Mendy et al., 2015a,b). Several studies have also shown a negative effect of *T. gondii* on cognition in adults and the elderly (Dickerson et al., 2014a; Gajewski et al., 2014; Hamdani et al., 2017; Mendy et al., 2015a,b; Nimgaonkar et al., 2016; Wyman et al., 2017).

Infections have been associated with cognitive and behavior changes in humans. Prenatal exposure to a range of infections and inflammatory responses may be associated with increased risk of adult schizophrenia (Khandaker et al., 2013). Infections in early childhood have been found to have negative effects on human cognition and increased risk of nonaffective psychosis. The association between infection and non-affective psychosis is mediated and moderated by IQ (Khandaker et al., 2018).

The immunological reaction to a parasite infestation may disrupt tryptophan metabolism, as parasite-infected cells secrete large amounts of kynurenic acid (KYNA) via indoleamine-2,3-dioxygenase (IDO)-mediated tryptophan degradation (Henriquez et al., 2009; McConkey et al., 2013). Latent *T. gondii* infection leads to the production of the rate-limiting enzyme IDO and tryptophan dioxygenase (TDO) in astrocytes (Campbell et al., 2014; Henriquez et al., 2009; McConkey et al., 2013; Nagineni et al., 1996). This leads to decreased levels of tryptophan, necessary for the growth and replication of *T. gondii,* but moreover, leads to the production of some harmful metabolites such as KYNA. Tryptophan is degraded by IDO to kynurenine, which is either metabolized to KYNA, an antagonist of the glutamate N-methyl-D-aspartate (NMDA) and nicotinic receptors (Campbell et al., 2014; Henriquez et al., 2009; Kessler et al., 1989) or hydroxylated to quinolinate, a potent NMDA neurotoxic agent (El-Defrawy et al., 1986). High levels of KYNA are found in the cerebrospinal fluid of schizophrenic individuals, and may plausibly cause cognitive disorders in schizophrenia (Henriquez et al., 2009). Tryptophan is also the essential precursor of serotonin, which is involved in depressive disorders. Hence, both dopaminergic and glutamatergic systems are affected by T. gondii and could represent the mediating factors between toxoplasmosis and psychiatric disease.

A causal relationship between serological evidence of exposure to *Toxoplasma* and psychiatric disorders has been well studied in individuals with schizophrenia (Flegr and Horáček, 2018; Hamdani et al., 2017; Sutterland et al., 2015; Torrey et al., 2012, 2007). We found a statistically significant association between serological evidence of exposure to *Toxoplasma* and schizophrenia or related disorders, compared to controls. An even stronger statistically significant association was observed between serological evidence of exposure to *Toxoplasma* and schizophrenia after excluding participants whose diagnosis preceded blood sample collection. This corroborates that *Toxoplasma* has a positive effect on the rate of schizophrenia and that *T. gondii* infection might be a contributing causal factor for schizophrenia. Similarly, a *meta*-analysis including all available studies analyzing the association between *T. gondii* infection and schizophrenia reported an increased odds ratio of 2·73 (Torrey et al., 2007). This level of association exceeds both the genetic and most other environmental risk factors for schizophrenia to date (Torrey et al., 2012), supporting the close relation between *T. gondii* infection and schizophrenia.

It has been found that individuals with higher titers of IgG class antibodies on *T. gondii* often show more severe symptoms of psychosis and a correlation between toxoplasmosis and increased mortality in

schizophrenic patients has been observed (Dickerson et al., 2007; Torrey et al., 2007). Interestingly, many anti-psychotic drugs commonly used in the treatment of schizophrenic patients have anti-*T. gondii* activity and may inhibit the replication and invasion of T. gondii in infected individuals (Gutiérrez-Fernández et al., 2015). It has been shown that schizophrenic patients treated with anti-psychotic drugs have lower levels of antibodies to *T. gondii* compared to untreated schizophrenic patients (Leweke et al., 2004). One could argue that the effect of anti-psychotic drugs in schizophrenic patients may be partly due to the inhibition of *T. gondii* activity.

Toxoplasma-associated behavior changes could result in decreased concentration and prolonged reaction time, which could increase the risk of traffic accidents. We found a very weak statistical association between *T. gondii* infection and risk of traffic accidents. Previous studies have found a 2–4 times higher risk of traffic accidents in individuals with *T. gondii* infection compared to non-infected individuals (Flegr et al., 2002; Flegr and Dama, 2014; Stepanova et al., 2017). Interesting, the only existing prospective cohort study on traffic accidents and toxoplasmosis found a significant association between traffic accidents and toxoplasmosis only in RhD-negative individuals, and not in RhD-positive individuals or in the non-sorted population (Flegr et al., 2009). The difference in RhD status could also apply to our study and may explain why we only found a very weak association between toxoplasmosis and traffic accidents. A recent systematic review and meta-analysis concluded that exposure to T. gondii significantly increases the risk of having traffic accidents (Gohardehi et al., 2018) which our results also supports. In addition, *T. gondii* infected individuals have been found also to have an increased risk of workplace accidents (perhaps due to decreased concentration and prolonged reaction times) (Alvarado-Esquivel et al., 2012) and of starting their own business (Johnson et al., 2018), but not of increased financial risk-taking (Lanchava et al., 2015).

Besides *T. gondii* infection, herpesvirus, such as CMV, infection has also been associated with psychiatric disorders, schizophrenia, mood disorders, decreased cognitive functioning, and suicide in seriously mentally ill individuals (Dickerson et al., 2017, 2014b; Hamdani et al., 2017; Prossin et al., 2015). Infections like CMV may cause alterations in the immune inflammatory cascades and have an impact on brain function through neuroinflammation (Tanaka et al., 2017).

In our study, CMV was statistically significantly associated with having any psychiatric disorder. An even stronger association was observed when including only individuals diagnosed after blood collection. CMV was more strongly associated with a more selected group of neurotic, stress-related, and somatoform disorders. This group might drive the observed effect in any psychiatric disorder, and a post hoc analysis showed that CMV infection had no impact on the risk of any psychiatry excluding F40-F48 (OR = 1·06, 95% CI 0·94–1·21, IRR = 1·41, 95%CI 0·99–2·00). Studies have showed that higher CMV-IgG levels are associated with increased anxiety, depression, vital exhaustion (lack of energy, increased irritability, and feelings of demoralization) and decreased SF-12 mental health (Phillips et al., 2008; Rector et al., 2014; Trzonkowski et al., 2004). Higher CMV-IgG levels reflect poorer immune control and reactivation of the virus (Glaser and Kiecolt-Glaser, 1994; Kuo et al., 2008; van Zanten et al., 1995), which may be triggered by psychological stress, representing a potential mechanism linking stress and immunity (Bosch et al., 2013).

Prossin et al. also found that a higher IgG concentration against CMV was associated with elevated mood states in bipolar disorders compared to healthy controls. In addition, CMV IgG was higher in individuals with bipolar disorder with elevated moods but not different in depressed moods when compared with euthymic bipolar disorder individuals (Prossin et al., 2015). We found a statistically significant association between CMV and mood disorder, but only in individuals diagnosed after the date of blood collection. In our analysis, we combined all diagnoses of mood disorders (ICD-10: F30-F39) into one category, whereas Prossin et al. focused only on bipolar disorder (ICD-10: F30-31) (Prossin et al., 2015). Our analysis was based on a more diverse group of mood disorders and is not suitable for demonstration of a statistically significant association between CMV and a specific mood disorder, such as bipolar disorder, due to the small numbers of cases (N = 57).

Previous studies have reported an association between inflammatory processes, such as infectious agents, and suicide. We found that CMV infection was statistically significantly associated with attempting or committing suicide. Taking only suicide or suicide attempts after blood donation into account, no association was observed, which might be due to the small number of individuals with suicide or suicide attempts after blood collection. Only two studies to date have addressed the association between CMV and suicide, and found an association between CMV and suicide attempts in individuals with serious mental illness (Dickerson et al., 2018, 2017). The observed association between CMV and suicide attempt may be due to the direct effect of the microorganisms altering the level of dopamine and other neurotransmitters, or due to the immune response altering the activity of toll-like receptors in response to CMV, which has also been shown to be altered in brains of individuals with completed suicide attempts (Pandey et al., 2014).

The effect of coinfection with *T. gondii* and CMV and the association with psychiatric disorders, suicidal behavior or traffic accidents did not influence the overall results.

Our study has several strengths. This case-control study is the largest serological study to date of *T. gondii* and CMV infection in relation to psychiatric disorders, self-violence and risk-taking behavior in a nation-wide population. Another strength of this study was that we accounted for temporality in the nested case-control study, i.e., the pathogen exposure should precede the outcome of interest to show possible causality. A limitation of this study was that we did not control for socio-economic factors, which may influence the probability of pathogen infection, development of psychiatric disorders, suicidal behavior, or involvement in traffic accidents. A study of the socio-demographic characteristics of the DBDS population showed that the middle to high income groups, but not the highest income group, had fourfold higher donor prevalence than the lowest income group (6.7% compared to 1.7%) and that social marginalization, as indicated by low income and being a male living without a woman, was associated with lower prevalence of blood donation (Burgdorf et al., 2017). We cannot rule out that socio-economic factors could potentially account for part or all of the observed causaleffect. The link between family history of psychiatric disorder and psychiatric disorders or suicidal behavior is well established (Dean et al., 2010). However, adjusting for parental history of psychiatric disorders did not influence the overall results. In this study, the prevalence of any psychiatric disorders was lower than the national lifetime risk of mental disorders (Pedersen et al., 2014). This may be due to the fact that the blood donor population is a highly selected population who are healthier than the general population, and since older blood donors are a highly selected group of individuals (the healthy donor effect), the generalizability to other settings may be limited.

In conclusion, our study finds that *T. gondii* infection might be a contributing causal factor for schizophrenia. Moreover, *T. gondii* infection was borderline significantly associated with traffic accidents. CMV infection may be a risk factor for developing any psychiatric disorder, especially neurotic, stress-related, and somatoform disorders, or for experiencing self-violence in the form of attempting or committing suicide. Although we did not control for socio-economic factors, which may have an effect on health outcome, we were able to account for temporality of pathogen exposure. Our findings support the growing scientific evidence linking pathogenic infection with serious psychiatric disorders. Routinely screening for *T. gondii* and CMV in populations with psychiatric disorders may identify novel stratification groups, which can be used to target treatment e.g. in combination with analysis of genetic risk factors. Likewise, targeting T. *gondii* or CMV infections

can provide novel therapeutic approaches as well as potential biomarkers to identify individuals at increased risk. A detailed understanding of the origin, mechanisms and outcomes of these pathogenic infections in relation to psychiatric disorders, self-violence and risk-taking behavior is necessary in order to improve detection and treatment.

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Declaration of interests

The authors report no conflict of interest. The authors alone are responsible for the content and writing of the paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bbi.2019.01.026.

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